To: Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Park Lawn Dr.
Room I-23
Rockville, MD 20857

RE: Docket No. 97N-0217

Dear Sirs:

Enclosed are two copies of the requested comments on Development of Options to Encourage Animal Drug Approval For Minor Species and For Minor Uses (9 pages) from:

William R. Lance, DVM PhD
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Sincerely,

Jo Dee Swets
Executive Assistant

97N-0217

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RESPONSE TO THE JUNE 23, 1997 FEDERAL REGISTER
Request for comments on Minor Species and Minor Uses Approval Option
Docket No. 97N-0217

BACKGROUND INFORMATION RELATIVE TO MINOR SPECIES.

FDA/CVM is to be commended for providing industry representatives the opportunity to respond to the questions posed in the 23 June Federal Register (FR62, 33781-83). The following background information will provide a review of some but not all the minor species and minor uses of drugs in major species that should be addressed in the proposed changes. The pharmaceutical needs for disease management, parasite control, sedation, anesthesia, reproduction enhancement or control, or production enhancement in minor species and for minor uses in major species are as diverse as the animal kingdom, the various conditions under which these species are maintained and their uses. Some minor species may be consumed as food, others have no food related issues, and minor uses are needed in major species, which may or may not be eaten. For the purpose of brevity comments relative to wild and exotic species are included in minor species.

Minor Species That May Be Consumed As Food

Examples are backyard and small commercial rabbitries, in which the rabbits provide a food source or small family income for a local specialty market. Pigeons as well may be raised as a family food source or be supplied to a local specialty food market. There are very small regional and emerging markets for ostrich, emu, ranched deer (fallow deer), North American elk, and bison. Additionally, there are markets for which excess animals from large game enclosures in the southwestern United States are periodically rounded up and processed for the specialty restaurant trade. In aquaculture, specialty markets such as cray fish and frogs also fall into this category. In the past, bait fish (minnows) were considered minor species and food since the sport fish caught by the bait would be consumed.

Minor Species Not Consumed

The minor species non-food segment is much larger and more diverse. This category can be subdivided into hooved stock, avian, aquaculture, marine mammals, and laboratory species. Under the category of minor species non-food hooved stock, there are several additional subdivisions, each with its own special needs and requirements. Some species of hooved stock are raised by private individuals for recreational purposes or for their by-products. Examples are llamas, elk, deer, and specialty breeds of sheep and goats, such as the mohair and fainting goats, etc.

Over 150 species of hooved stock are maintained in zoos and game parks. These animals never enter the food chain, may have extremely high monetary and intrinsic value, may represent rare and endangered species breeding stock and are maintained under confinement. The wild and free ranging endemic North American species such as white

tailed deer, elk, moose, pronghorn, etc. are another category. These may or may not be consumed, depending upon local conditions and regulations. If hunting is allowed, then food safety may be an issue if drugs are used during a hunting season. These species have special needs for safe sedation, anesthesia, disease management and in some instances (white tailed deer) need pharmaceutical tools for population control.

In the carnivore category, there are large carnivores such as bears, tigers and lions in private collections, as well as exhibition parks that have specialized pharmaceutical needs for optimum sedation and restraint. Small carnivores such as ranched mink and fox are raised for their fur production and typically are small private enterprises that are sources of family income on small acreages. Some small carnivores kept as pets such as domestic ferrets are becoming increasingly common in households in the United States today.

Other small carnivores such as raccoons, foxes and coyotes may have needs for safe sedation, anesthesia or possible requirements for population control. The issue of pharmaceutical applications for population control of nuisance small and rodent (prairie dogs) carnivore species in urban or recreational areas through reproduction suppression or disruption is a new but very real emerging need.

Under the non-food avian classification, examples are racing and show pigeons; backyard exotic fowl such as pea fowl, exotic species of turkey, pheasants, show chickens, members of the psittacine group (parrots, macaw, etc.), finches and canaries maintained as pets, plus the numerous exotic species maintained in zoos and scientific collections around the United States. Also within the avian category are the various raptors (eagles, hawks, etc.) maintained in wildlife rehabilitation centers and in zoological collections. Again, this group has all the basic pharmaceutical needs of the others.

In the non-food aquatic environment and aquatic species group are marine mammals maintained in zoological gardens and exhibits. Marine mammals, although extremely limited in numbers in exhibits and research facilities around the country, have an extremely high monetary and extrinsic value to those institutions that maintain them. Marine mammals experience a high prevalence of external and internal mycotic conditions. Also in the aquatic category are fish for hobby aquaria and the production farms that supply the hobby aquarium trade. In aquaculture, there are many situations where brood fish are not eaten but are maintained to supply eggs and fingerlings for sport fisheries as well as individuals propagated to maintain rare and endangered species. In many instances, the brood fish are collected, administered sedatives to enable safe handling and hormones to enhance reproduction. Examples of this are the large Atlantic sturgeon and the Gulf Coast striped bass. The individual fish weighs from 25 to 100 kilograms and the use of anesthetics and sedatives is the only method to safely handle these animals to prevent damage to themselves and the fishery biologists. In the large exhibit aquariums around the United States such as the National Aquarium in Baltimore, fish in these environments have pharmaceutical needs unique to their situation and institutional maintenance.

The final subcategory under minor species are the laboratory species, such as laboratory rabbits, rats and mice. In laboratory animal medicine there is a constant search for better sedatives, anesthetics and combinations to control pain and discomfort to a laboratory animal during research procedures. This is an extremely limited use but very, very important to laboratory animal medicine and animal welfare.

Minor Use In Major Species

In almost any major species one could name, there are needs for pharmaceuticals to control limited diseases, modify reproduction or specialized sedation or anesthesia needs. In the major species there are always minor use needs as in equines for various hormonal combinations and delivery systems to modify or control reproductive function.

As mentioned earlier the pharmaceutical needs of these various categories range from anti-fungal therapeutics for marine mammals, safe and reliable drug combinations for sedation, anesthesia and transport for all species, parasite control, enhancement of reproductive performance such as stimulation of brood fish in aquaculture, rare and endangered species, or disruption of reproduction patterns in wild and free ranging nuisance species.

RESPONSE TO FEDERAL REGISTER

It is recommended that the criteria found in Section 514.1(d)(1)(i)(b), regarding minor species or minor use be expanded to include conditions other than disease such as applications for production enhancement, reproduction modification, sedation or anesthesia in minor species or similar minor uses in a major species. There are pharmaceutical applications needed in minor species or minor uses in major species that do not address disease problems, but are very important to the management of a minor species or as a minor use in major species.

B. Creating Additional Statutory Authority.

1. Should there be different standards for target animal safety and effectiveness of new animal drugs intended for use in minor species or for minor uses?

Safety and effectiveness is always of prime importance to the owners of any animal, the veterinarian treating that animal, as well as a pharmaceutical company producing the drug for that animal. Protocols required for demonstrating safety and effectiveness in minor species must consider the actual conditions of use of the drug in the target species as well as the availability of test animals for conducting such studies. In the case of wild and exotic species it would be cost prohibitive to do safety and effectiveness in every species of African antelope. It is suggested that the Center permit a broader application of data to include family groups, such as exotic Cervidea, Bovidea, etc. rather than to individual species and to permit broad labeling as such.

2. Should there be different standards for human food safety for new animal drugs intended for minor species and for minor uses?

Human food safety is always important. In applications where the drug is used in early life stages of the species, such as in young rabbits or food fish species, FDA/CVM should take a rational approach on the risk of that drug having any impact in the final edible form of the species. The probability of a drug used to treat incubating eggs of a food fish having residues or impact in the individual fish as it enters the food chain some 18 to 36 months later must be extremely low.

3. If so, what should those standards be?

There cannot be one standard that would cover all minor species or minor use applications. There should be language in the new regulations that empower the FDA/CVM personnel as responsible scientists, working in concert with the end user and the pharmaceutical sponsor/manufacturer to agree upon a standard that would allow the drug to be used with a mutually agreed acceptable level of risk.

4. Should the standards be the same for all minor species and uses?

As stated in the background information, no standard could be made for all minor species applications due to the extreme diversity of species and conditions of use. There could be a set of standard applications for broad categories such as for use in non-food and ornamental fishes and another only applicable to reproductive management in zoos or free ranging wildlife, etc.

5. Should products be labeled to reflect the use of different standards?

Yes, the end user should be made aware that the approval was made under a different level of testing than for traditional domestic species.

6. If the Act were amended to permit FDA to approve an animal drug for minor species or use under different standards, how would appropriate doses be determined and how would residue depletion withdrawal times for food animals be determined?

This is a rather difficult question. For any non-food species, it is recommended that a dose be allowed that is simply an effective dose, as opposed to requiring a minimal effective dose. This would reduce the tedious and expensive task of documenting the minimal effective dose.

Regarding residue depletion withdrawal times, if there is a reasonably compatible domestic species (same family) in which a similar (not identical) compound has been approved, then possibly extrapolation of data could be used with the inclusion of a 3x safety factor for determining withdrawal times for food animals. The determination and cost associated with residue depletion studies and validation of associated analytical techniques is extremely expensive.

7. Would sponsors and users accept conditional approval with post-market surveillance as a trade off for requiring less in the way of pre-market target animal safety and effectiveness study for new animal drugs for minor species or minor uses?

The answer to this is a resounding yes. The companies which serve these small niche specialized uses can easily trace and monitor distribution of product.

8. Should a drug approved under such mechanism bear labeling that reflects its status?

Yes, I believe that this is appropriate and acceptable to industry.

9. Should the act be amended to allow FDA to accept foreign reviews or approvals for minor animal species or minor use?

This is a definite and strong yes. There are many drugs used in minor species in foreign countries that have excellent data packages and long histories of use in the foreign countries that FDA/CVM could and should rely upon in their approval process.

10. Should the current statutory standard for new animal drug approval intended for minor species or minor uses or any alternative standard be implemented through a primary review process external to the agency? If so, how might this process be administered and who should pay for the external review?

The authorization or implementation of a primary review process external to the agency, similar to the NAS/NRC DESI program, could provide several cost effective alternatives for FDA/CVM, industry and the end user. In the areas of minor species, there are veterinarians and veterinarian scientists that have first hand experience in the target species and are sensitive of the needs of the associated interest group or industries, as well as the economic implications relative to the use of pharmaceuticals in that target species. It would be an advantage to FDA/CVM to be able to legally utilize these individuals as external review resources of the data packages and the labeling associated with the approval. This process might be administered through a single individual within the Center. Review panels could be developed within associations, such as the American Association of Zoo Veterinarians, the Association of Avian Veterinarians, Am. Assoc. of Small Ruminant Practitioners, etc. The cost of the external review process could possibly be shared between FDA/CVM, the respective industry groups that need the particular pharmaceutical and the pharmaceutical company seeking to supply that need.

11. How should Congress or FDA determine whether reviews or approvals of a particular country or countries are acceptable as a basis of approval for uses in minor species or for minor uses?

FDA/CVM could base its determination of acceptance upon its experience with a given country or economic group. With the trend towards harmonization of regulatory processes, it would be very easy to determine which country or group of countries, such as the Nordic group EEU, NAFTA, etc., have comparable approval standards.

12. Could determination of animal safety and effectiveness by expert panels or compendia be used to support drug approval for minor species or minor use?

Yes. Panels from such groups as American College of Laboratory Animal Medicine, American Association of Zoo Veterinarians, American Avian Veterinarians, American Association of Wildlife Veterinarians, and the Association of Small Ruminant Practitioners would be of value.

13. If so, what information would serve as a basis for such determination?

The information could be an effective dose determination study demonstrating the field effectiveness of that dose combined with a very minimal safety study.

14. Should the determinations of these panels or other information be used to issue monographs or similar standards?

Yes, set it up like CDER for the human drug monograph.

15. Who would draft monographs or similar standards and why?

The experts in the field, again similar to the NAS/NRC DESI program.

C. Administrative and Regulatory Change

16. Should there be different standards for manufacturing of drugs for minor species or minor uses?

This is an absolute must. Drugs produced for minor species or minor uses are produced in extremely small quantities. The requirement for most specialized sterile injectables for minor species usage is often less than 1,000 vials per year. If the full weight of current good manufacturing practices (cGmp's) currently applied to human and veterinary drugs is applied to pharmaceuticals for minor species, the regulatory cost will certainly prohibit production. The level of validation and controls required should be adequate to ensure that a safe and effective product is consistently produced but the level and rigor of process control should remain appropriate to the batch sizes, frequency of production and the conditions of use.

17. If so, what should those standards be?

Those standards should be arrived at through dialogue from FDA/CVM, the drug sponsor, and the FDA District inspectors. District inspectors must be made aware of the special conditions relating to these products.

18. Should the products be labeled to reflect the use of different manufacturing standards?

If the end product testing determines the final product to be safe and effective, there should be no difference in labeling.

19. Would a strategy similar to those used by the agency to facilitate drug approval for some aquatic species be successful if extended to other minor species?

No. In this respondents opinion, the process utilizing information collected and generated by end users, as well as the centrally organized CVM operated field education programs to promote end users as potential INAD sponsors has not accelerated drug approval for aquatic species. In some cases it has slowed the process down through additional levels of review and coordination.

D. Creating Incentives

20. Would economic incentives, such as tax breaks, grants, and periods of market or label exclusivity, encourage the pursuit of approvals of supplemental approvals for labeling modifications for minor species or minor uses?

From the industry point of view, periods of market or label exclusivity would be the minimum incentive required to encourage pursuit of additional approvals. Economic incentives (tax breaks) and grants would be most helpful.

21. Would different kinds of incentives be appropriate for different classes of new animal drugs?

Yes, the industry would need considerable incentives to develop drugs, for example for hobby-owned tropical fishes. The development of production drugs for fish intended for human consumption would need direct financial support to defray the expense of drug withdrawal and food safety studies.

22. Should a program similar to the U.S. Department of Agriculture's National Research Support Program #7, which currently funds studies fro minor use therapeutic uses for food and fiber-producing animals, be developed for wildlife and zoo animals and/or for production uses?

The answer to this question is a resounding yes. Historically the scope of NRSP-7 has been adequate and proper but the new emerging needs are in minor species and minor use in major species, in the category of wildlife, zoo, non-traditional species and production uses.

23. Could and should philanthropic, public interest, or other not-for-profit organizations be encouraged to fund research for the development of new animal drugs intended for use in minor species or for minor uses?

Yes. There are organizations that have an interest in a species or a certain application that the mechanism should be made available where they could fund research. The one thing that these public interest groups would need to know is the level of financial commitment required to get the required approval. This would call for a clear

definition of the FDA requirements for the minor species or minor use applications in an almost contractual form before the project is started.

24. Are there mechanisms other than the new animal drug approval process and extra label uses of animal and human drugs under the AMUCA that could enhance drug availability for minor species and for minor uses?

No response.

E. Extending Existing Legal Authority

25. Would legislation be desirable to extend the AMDUCA to permit extra label use of medicated feeds or reproductive hormones and implants?

Yes. Approval versus extra label use would require generation of data that would support the approval, where as extra label use requires a veterinarian based upon training knowledge and understanding of the drug to make a professional determination and accept the responsibility for the drugs use. The approval process requires the generation of data that can be relied upon by the Center for determining withdrawal times, precautions, etc., for products in minor species or minor use in a major species. This requires considerable investment of resources by FDA/CVM as well as industry.

Additional Comments

As correctly stated in the Federal Register requesting comments on this issue FDA/CVM upper management has attempted to encourage submissions for minor species and minor uses. Unfortunately, this encouragement has not resulted in any effective change in review procedures or policies at the lower staff levels. Unless there is radical change in FDA/CVM's actual implementation of current review procedures, safety/efficiency requirements, CMC requirements (Chemistry Manufacturing Controls) etc., of new pharmaceuticals for minor, wild and exotic species industry will not make the intellectual and capital investment necessary to bring new submissions forth. Likewise, without major revision in the cGMP requirements of FDA/CVM and the FDA Districts regarding minor species / minor use pharmaceuticals even those currently available maybe withdrawn from the United States markets due to crushing regulatory overburden.

Respectfully Submitted,

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